Published in final edited form as:

*Cancer Epidemiol Biomarkers Prev*. 2011 May ; 20(5): 854–858. doi:10.1158/1055-9965.EPI-10-1041.

# Soy Food Consumption and Breast Cancer Prognosis

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## Abstract

**Background—**Contrary to earlier clinical studies suggesting soy may promote breast tumor growth, two recent studies demonstrate that soy-containing foods are not adversely related to breast cancer prognosis. Using data from the Women's Healthy Eating and Living (WHEL) study, we examined the effect of soy intake on breast cancer prognosis.

**Methods—**3088 breast cancer survivors, diagnosed between 1991 and 2000 with early stage breast cancer and participating in WHEL were followed for a median of 7.3 years. Isoflavone intakes were measured post-diagnosis using a food frequency questionnaire (FFQ). Women self-reported new outcome events semi-annually which were then verified by medical records and/or death certificates. Hazard ratios (HR) and 95% confidence intervals (CI) representing the association between either a second breast cancer event or death and soy intake were computed, adjusting for study group and other covariates using the delayed entry Cox proportional hazards model.

**Results—**As isoflavone intake increased, risk of death decreased (p for trend=0.02). Women at the highest levels of isoflavone intake (>16.3 mg isoflavones) - had a non-significant 54% reduction in risk of death.

**Conclusions—**Our study is the third epidemiological study to report no adverse effects of soy foods on breast cancer prognosis.

**Impact—**These studies, taken together, which vary in ethnic composition (two from the US and one from China) and by level and type of soy consumption, provide the necessary epidemiological evidence that clinicians no longer need to advise against soy consumption for women diagnosed with breast cancer.

## Introduction

Soy foods, a major source of phyto-estrogens demonstrate both anti-estrogenic and estrogen-like properties. Many studies have demonstrated that soy consumption may protect against

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breast cancer, while in contrast, other studies have shown that isoflavones, the major component of soy, enhance the proliferation of breast cancer cells in vitro(1), promote mammary tumor growth in rats(2), and possibly interfere with the effectiveness of Tamoxifen(3, 4). As a result, clinicians treating women with breast cancer frequently caution them to either avoid soy foods entirely or use them in moderation(2, 5, 6).

To add to the uncertainty, two recent epidemiological studies examining breast cancer survivors, one in Asian women from the Shanghai Breast Cancer Survival Study (SBCS)(7) and one in US women from the Life After Cancer Epidemiology study (LACE)(8), suggest that soy-containing foods do not adversely affect breast cancer prognosis, do not counteract the benefits of Tamoxifen and may, in fact offer some potential benefits in decreasing risk of recurrence or death from breast cancer. Before clinical recommendations can be made, these findings need to be replicated in other large cohorts with longer follow-up. We have explored this question further in secondary analyses using data from the Women's Healthy Eating and Living (WHEL) study, a randomized controlled trial of a high fruit/vegetable/fiber and low fat dietary intervention in early stage breast cancer survivors in the US.

## Materials and Methods

The WHEL study population has been previously described(9). Briefly, 3088 breast cancer survivors diagnosed between 1991 and 2000 who participated in a dietary intervention trial were followed throughout and after completion of the trial which ended in 2006. Enrolled participants were diagnosed with and completed treatment (within the previous 4 years) for Stage I, II or III (AJCC VI classification) invasive breast cancer. Participants were 18-70 years of age and had no evidence of disease within the 12 months prior to study enrollment. During semi-annual telephone interviews, women were queried regarding the occurrence of new outcome events. Any report of a breast cancer event was confirmed by medical records and/or death certificates and oncologist review. Finally, we searched the National Death Index using Social Security Number, name, and date of birth to confirm cause of death.

Women included in this study had a median follow-up of 7.3 years from the time of enrollment. Soy intake (mg isoflavones) was measured post-diagnosis (median 2 years, range: 2 months to 4years) at study entry using the Arizona Food Frequency Questionnaire, a 153-item, semiquantitative, scannable questionnaire(10, 11) which included specific line items for "Meat Substitutes (such as Tofu, Veggie Burgers)," and "Soy Milk" as well as an opportunity to include other soy food items on the "additional foods" list portion of the FFQ. Modified from the Block-National Cancer Institute Health Habits and History Questionnaire the AFFQ which has previously been validated against both 4-day food records(11)and 24 hour recalls(10) and elicits information regarding the usual foods consumed and the frequency of consumption, using age- and gender-specific estimates of portions estimated as small, medium, or large.

Additionally, information on soy supplement use since diagnosis was obtained by a separate questionnaire(12) asking respondents about the frequency and duration of use using an extensive list of supplements and herbs and allowing participants to report their supplements not listed on the pre-determined list in an open-ended question. A yes/no use variable was

created since the responses indicating the frequency and duration of soy supplement use were low.

Daily isoflavone intake, derived from totaling isoflavone intake across all line items in the FFQ were generated using the USDA-Iowa State University Database on the Isoflavone Content of Foods(13). Isoflavone contents of foods in the USDA database were collected from scientific articles published in refereed journals and were generated by extensive sampling of soy-containing foods and subsequent analysis at Iowa State University.

### Data Analyses

Women were divided into four groups with the highest category (upper 5$^{th}$ percentile: 6.3-86.9mg/day) representing intakes similar to those consumed in Asian populations. Delayed entry multiple Cox proportional hazards models(14) were developed and hazard ratios (HR) and 95% confidence intervals (CI) representing the association between either a second breast cancer event or all-cause mortality and level of soy intake were computed. A second breast cancer event included both local and distant recurrences as well as new breast primaries. All cause mortality included death due to any cause, although 81% of the deaths were due to breast cancer. The models were adjusted for randomization group, soy supplement use and other demographic and clinical covariates known to be associated with breast cancer outcomes. Score tests were used to assess trends across quintiles. Residual plots were used to examine model fit. Likelihood ratio tests were used to examine interactions between isoflavone intake and each of tamoxifen use and ER/PR status, to examine if these factors modified the association between isoflavones and outcomes. The software package R was used for all statistical analysis(15).

## Results

Baseline isoflavone intakes did not differ between the intervention and control groups. Among women in the intervention and control groups, 19.2% and 20.8 % respectively consumed greater than 10.1mg of isoflavones daily (data not shown). Isoflavone intake differed by age, race/ethnicity and education but did not differ by Tamoxifen use, hormone receptor status or menopausal status. Younger women, Asians and women with a college degree or higher were the most likely to consume soy in the upper category (Table 1). Isoflavone intake was unrelated to the risk of a second breast cancer event overall or within strata of women defined by hormone receptor status or whether they ever used Tamoxifen (Table 2). Furthermore, no significant increased or decreased risk was associated with any level of intake within strata (Table 2). In contrast, for overall mortality: risk of death tended to be lower as isoflavone intake increased (p for trend=0.02). Women at the highest levels of isoflavone intake (>16.3 mg isoflavones- equivalent to at least ½ cup soymilk or 2 oz tofu each day) had a non-significant 54% reduction in risk of death compared to the lowest quintile of soy intake. Although the interaction between soy intake and Tamoxifen use on mortality was not statistically significant (Table 2), the observed trend toward lower mortality with increased soy appeared stronger in women who had ever used Tamoxifen (p for trend=0.05). The trend toward lower mortality with increasing soy did not differ by hormone receptor status of the tumor. Sensitivity analyses were conducted by repeating the

analysis restricted to the subgroup of women who were currently (at baseline) taking Tamoxifen (N=1642); the results did not change (data not shown).

## Discussion

Our study is now the third epidemiologic study in the recent past to report no adverse effects of soy food intake on breast cancer recurrence(7, 8) or total mortality(7) either alone or in combination with Tamoxifen(7, 8). Contrary to soy being harmful, these recent reports to varying degrees, suggest possible benefits for breast cancer survivors.

Although the mean soy intake in the WHEL population is much lower than that observed among Chinese women in the SBCS(7), the suggested protective associations seen with total mortality for women in WHEL at the highest soy intake level, are comparable to what was seen for Chinese women consuming similar levels of isoflavones. Also similar to results from both the SBCS study(7) and the LACE study(8), the largest benefits associated with soy consumption, in our study were seen in women who used Tamoxifen. Continued research is needed to further understand and confirm these relationships since in WHEL power to detect associations at the highest level of soy intake was limited.

Strengths of the WHEL study include being one of the few existing studies of early-stage breast cancer survivors with long-term follow-up on both recurrence and survivial as well as information on post-diagnoisis soy food intake. Although, our analyses relied on self-report of soy food intake from the Arizona FFQ, several validation studies have reported that assessment of soy intake by food frequency questionnaires (FFQ) that use soymilk and tofu alone correlate well with isoflavone biomarkers either in blood or urine(16–19). In one study of US adults(17)where they compared a soy-specific 40 item FFQ to the more general 122 item WHI FFQ and examined intakes from both with plasma concentrations, they found that isoflavone intake was highly correlated between the two FFQ instruments (r=0.84) and that isoflavone intake derived from both instruments were significantly correlated with plasma concentration of isoflavones. They also found that soymilk and tofu were the two major contributors to isoflavone intake and accounted for approximately 40% of total intake.

Because the WHEL cohort consists of early-stage breast cancer survivors who were enrolled on average 2 years after diagnosis, our results are not generalizable to women diagnosed with advanced-stage breast cancer and apply only to women who have survived, on average, 2 years since diagnosis.

In summary, we found no adverse associations of soy food consumption with breast cancer prognosis, even at levels similar to those consumed in Asian populations. Our study and the two previous epidemiological studies, taken together, which vary in racial/ethnic composition (two from the US and one from China) and by level and type of soy consumption, provide the necessary evidence that clinicians no longer need to advise against soy food consumption for women diagnosed with breast cancer.

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*Cancer Epidemiol Biomarkers Prev*. Author manuscript; available in PMC 2020 July 14.

**Table 1**

Number and Percent of Women Enrolled In WHEL across Isoflavone category by Demographic, Medical and Tumor Characteristics

| | Soy Isoflavone Intake(mg/day) | | | | |
|---|---|---|---|---|---|
| **Baseline Characteristics** | **Level 1 [0-0.7] median= 0 n (%)** | **Level 2 (0.7-1.01] median= 0.3 n (%)** | **Level 3 (1.01-16.33] median= 4.8 n (%)** | **Level 4 (16.33-86.9] median= 26.7 n (%)** | **P-value*** |
| **Age (years)** | | | | | 0.008 |
| < 45 | 182(37.9) | 192(40) | 80(16.7) | 26(5.4) | |
| 45-54 | 440(39) | 441(39.1) | 180(15.9) | 68(6) | |
| 55-60 | 179(37.9) | 194(41.1) | 75(15.9) | 24(5.1) | |
| >=60 | 294(44.9) | 267(40.8) | 75(11.5) | 19(2.9) | |
| **Race/Ethnicity** | | | | | <0.001 |
| White | 910(39.0) | 951(40.7) | 350(15) | 123(5.3) | |
| Black | 69(65.7) | 26(24.8) | 9(8.6) | 1(1) | |
| Hispanic | 91(61.1) | 42(28.2) | 12(8.1) | 4(2.7) | |
| Asian | 8(9.5) | 45(53.6) | 27(32.1) | 4(4.8) | |
| Other* | 17(26.6) | 30(46.9) | 12(18.8) | 5(7.8) | |
| **Education** | | | | | <0.001 |
| Some college | 625(50.2) | 455(36.6) | 128(10.3) | 36(2.9) | |
| College degree or higher | 470(31.5) | 639(42.8) | 282(18.9) | 101(6.8) | |
| **Menopausal Status** | | | | | 0.189 |
| Post or Perimenopausal | 985(40.6) | 967(39.9) | 357(14.7) | 117(4.8) | |
| Premenopausal | 108(35.3) | 126(41.2) | 52(17) | 20(6.5) | |
| **Baseline Tamoxifen Use** | | | | | 0.321 |
| Current | 646(39.3) | 668(40.7) | 247(15) | 81(4.9) | |
| Never | 376(42.5) | 334(37.8) | 128(14.5) | 46(5.2) | |
| Past | 59(33.9) | 81(46.6) | 27(15.5) | 7(4) | |
| **ER/PR status** | | | | | |
| ER+ or PR+ | 835(38.9) | 865(40.3) | 331(15.4) | 113(5.3) | 0.127 |
| ER−/PR− | 238(43.6) | 214(39.2) | 74(13.6) | 20(3.7) | |
| Stage | | | | | 0.25 |
| I | 430(40.5) | 438(41.2) | 143(13.5) | 52(4.9) | |

| Baseline Characteristics | Soy Isoflavone Intake(mg/day) | | | | P-value* |
|---|---|---|---|---|---|
| | Level 1 [0-0.7] median= 0 n (%) | Level 2 (0.7-1.01] median= 0.3 n (%) | Level 3 (1.01-16.33] median= 4.8 n (%) | Level 4 (16.33-86.9] median= 26.7 n (%) | |
| II | 495(39.5) | 489(40.0) | 202(16.1) | 68(5.4) | |
| III | 170(40.6) | 167(39.9) | 65(15.5) | 17(3.3.) | |
| **Isoflavone Supplements**** | | | | | 0.001 |
| Yes | 17(29.3) | 16(27.6) | 18(31) | 7(12.1) | |
| No | 1078(40.3) | 1078(40.3) | 392(14.6) | 130(4.9) | |

*Pacific Islander, American Indian/mixed race

**p-value for differences of isoflavone intake between strata within category

*Cancer Epidemiol Biomarkers Prev*. Author manuscript; available in PMC 2020 July 14.

**Table 2**

Adjusted* Hazard ratios (HRs) and 95% CI's for Breast Cancer Recurrence and Mortality for levels of Isoflavone Intake at Baseline (all women and stratified by Tamoxifen use and hormone receptor status) for Women enrolled in WHEL

| | N | Number of New Breast Cancer Events | HR(95% CI)for New Invasive Breast Cancer Event** (n=448) | Number of Deaths | HR(95% CI) for Overall Mortality (n=271) |
|---|---|---|---|---|---|
| **All Women (n=2736)** | | | | | |
| *Total Isoflavones(mg/day)* | | | | | |
| Level 1 (0-0.07) | 1095 | 190 | Reference:1 | 133 | Reference:1 |
| Level 2:(0.07-1.01] | 1094 | 167 | 0.89(0.72-1.11) | 95 | 0.75(0.57-0.99) |
| Level 3:(1.01-16.33] | 410 | 73 | 0.99(0.75-1.32) | 37 | 0.79(0.54-1.15) |
| Level 4:(16.33-86.9] | 137 | 18 | 0.78(0.46-1.31) | 6 | 0.46(0.2-1.05) |
| | | | P for trend = 0.47 | | P for trend=0.02 |
| **Women who used Tamoxifen(n=1816)** | | | | | |
| *Total Isoflavones (mg/day)* | | | | | |
| Level 1 (0-0.07) | 705 | 112 | Reference: 1 | 79 | Reference:1 |
| Level 2:(0.07-1.01] | 749 | 106 | 0.91 (0.69 -1.21) | 64 | 0.79(0.56-1.12) |
| Level 3:(1.01-16.33] | 274 | 44 | 0.97(0.67 -1.41) | 23 | 0.81(0.5-1.3) |
| Level 4:(16.33-86.9] | 88 | 8 | 0.59 (0.27 -1.29) | 2 | 0.26(0.06-1.08) |
| | | | P for trend=0.35 | | P for trend=0.05 |
| **Non-users of Tamoxifen(n=884)** | | | | | |
| *Isoflavones (mg/d)* | | | | | |
| Level 1 (0-0.07) | 376 | 77 | Reference: 1 | 53 | Reference:1 |
| Level 2:(0.07-1.01] | 334 | 58 | 0.82(0.57-1.17) | 28 | 0.61(0.38-0.99) |
| Level 3:(1.01-16.33] | 128 | 28 | 1.09(0.69-1.71) | 13 | 0.79(0.42-1.49) |
| Level 4:(16.33-86.9] | 88 | 10 | 0.96(0.46-1.99) | 4 | 0.68(0.24-1.99) |
| | | | P for trend=1.0 | | P for trend=0.20 |
| **Interaction between Tamoxifen and Isoflavones** | | | P for interaction =0.54 | | P for interaction=0.45 |
| **Women with tumors that were ER+ or PR+ (n=2144)** | | | | | |
| Level 1 (0-0.07) | 835 | 137 | Reference:1 | 93 | Reference:1 |
| Level 2:(0.07-1.01] | 865 | 125 | 0.9(0.7-1.16) | 70 | 0.76(0.55-1.05) |
| Level 3:(1.01-16.33] | 331 | 58 | 1.06(0.77-1.46) | 30 | 0.91(0.59-1.39) |

| | N | Number of New Breast Cancer Events | HR(95% CI)for New Invasive Breast Cancer Event** (n=448) | Number of Deaths | HR(95% CI) for Overall Mortality (n=271) |
|---|---|---|---|---|---|
| Level 4:(16.33-86.9] | 113 | 14 | 0.84(0.47-1.51) | 3 | 0.31(0.1-0.98) |
| | | | P for trend = 0.83 | | P for trend=0.07 |
| **Women with tumors that were ER−, PR− (n=546)** | | | | | |
| Level 1 (0-0.07) | 238 | 50 | Reference:1 | 38 | Reference:1 |
| Level 2:(0.07-1.01] | 214 | 39 | 0.78(0.5-1.22) | 24 | 0.62(0.36-1.07) |
| Level 3:(1.01-16.33] | 74 | 14 | 0.79(0.42-1.49) | 7 | 0.46(0.19-1.1) |
| Level 4:(16.33-86.9] | 20 | 3 | 0.62(0.19-2.03) | 3 | 0.86(0.25-2.9) |
| | | | P for trend = 0.25 | | P for trend=0.10 |
| **Interaction between receptor status and isoflavones** | | | P for interaction=0.91 | | P for interaction=0.31 |

*Models adjusted for stage, grade, ER/PR status, menopausal status, chemotherapy treatment, radiation, age, education, race, soy supplements intervention group, presence of hot flash symptoms and their interaction; the unstratified model was also adjusted for Tamoxifen use; the model subset to women not taking Tamoxifen did not adjust for race due to small cell sizes.

**New breast cancer event includes an invasive breast cancer recurrence or a new invasive primary breast cancer